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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,409	01/23/2002	Maria Palasis	104914.132US2	1618

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,409	PALASIS, MARIA	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-54* is/are pending in the application.

4a) Of the above claim(s) *4-11,16,18,20-22,26-37,41-48,52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15,17,19,23-25,38-40,49-51 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments of 6/16/05 and the response and amendments of 7/1/05 are entered.

Claims 12, 15, 17, 19, 26, 23-24, and 54 are amended.

Claims 4-54 are presently pending.

Note: Change in Art Unit and SPE

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

Note: proper claim identifiers

Applicant is notified that the proper use of amended claims that are withdrawn is also to note the amended status, i.e., by using the identifier "Withdrawn – Currently Amended". It is noted that claim 26 is withdrawn, and has been amended but is simply labeled "Withdrawn". Please use proper terminology in the future.

Election/Restrictions

Applicant's election of Group IV and the species of (i) VEGF and (ii) stem cells in the reply filed on 6/16/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is further noted that Applicant listed claim 37 as a claim that is not withdrawn, however, such claim was subject to a species election, in which Applicant elected VEGF (Restriction Requirement of 4/19/05, p. 5, paragraph 3).

Claims 4-11, 16, 18, 20-22, 26-37, 41-48, and 52-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/16/05.

Claims 12-15, 17, 19, 23-25, 38-40, 49-51, and 54 are presently considered.

Prior Rejections of Claims

In light of the prosecution history and the prior Examiner's restriction requirement being improper, and further in light of the fact that Applicant has elected a substantively different group from that which was previously considered, all prior rejections on the pending claims are withdrawn, and the following new rejections are applied.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12-13 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31 and 35 of copending Application No.

10/623,20. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 12-13 encompass a method of delivery of an agent comprising cells to an ischemic/diseased heart comprising the administration of a therapeutic agent to normal tissue in the heart.

Claims 31 and 35 of Application No. 10/623,205 encompass the administration of peripheral blood stem cells to an ischemic or diseased heart.

Hence, these claims encompass the same subject matter, except that the subject Application encompasses anywhere in the heart, not just normal tissue.

Moreover, the Artisan would have been motivated from the specification of 10/623,205 to administer it to normal tissue because the Application does not teach that administration to the ischemic tissue is important, and further it teaches that it may also be administered by perfusion (paragraph 0033), and as such, it is clear that location is not important.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 17, 19, and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15, 17, and 19 each recite the term "cells capable of producing an angiogenic factor". All cells are capable of producing an angiogenic factor. To wit, even mycobacteria, if transformed with a transgene are capable of producing an angiogenic factor, and all the cells of all animals with a circulatory system contain the genes encoding all the angiogenic factors; hence, all these cells are also capable of producing an angiogenic factor. Therefore, because Applicant has not claimed a cell, but instead, that subset of cells which are capable of producing an angiogenic factor, this rejection is made because the metes and bounds of the limitation are not clear to the Examiner.

Claims 23-25 are rejected for depending from base claims that lack clarity, and for not overcoming the lack of clarity in such base claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14, 15, 17, 19, 23-25, 38, 39-40, and 49-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the intramyocardial delivery of autologous mesenchymal stem cells modified *ex vivo* to express an angiogenic factor via a constitutive promoter operatively linked to a sequence encoding an angiogenic factor, to normal tissue adjacent to ischemic tissue in the myocardium, does not reasonably provide enablement for the administration of any cell type or delivery of such cells to tissues not adjacent to the ischemic tissue or the absence of a transgene, any non-constitutive promoters or the use of any transgene in any cell type. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

It is noted that this is a weighting of factors, and not an 8-prong test; therefore, any single factor may outweigh all other factors, and other non-listed factors may outweigh the listed factors.

The Breadth of the Claims

Applicant's claims encompass many methods requiring delivery of any angiogenic factor or any cell capable of expressing an angiogenic factor, and particular claims to simple delivery of cells, each delivered to normal myocardial tissue in a heart, and such tissue may be adjacent to ischemic tissue.

Moreover, Applicant's claims require all require ischemic tissue, which is taught to be treated in the specification by the methods, and no other reason for delivery of such agents is given, hence, even for the simple delivery methods, not requiring any treatment, the only reason for performing the methods is for treatment of ischemic tissue in the myocardium.

These cell types and locations of delivery are broad, and as such, the specification, in light of the Art, must cover a wide range of knowledge, so that the Artisan would not have to perform undue experimentation to determine the efficacious embodiments.

The Amount of Guidance and Direction Provided by Applicant

Applicant's specification broadly discusses cardiovascular diseases, myocardial gene therapy, and the surprising finding that a favorable functional response has been found by Applicant when an angiogenic agent is directly injected into normal myocardium adjacent to an ischemic zone, compared to the direct delivery to the ischemic zone which is known in the art (pp. 1-2).

A brief summary of the invention is then provided, roughly covering claim language (pp. 2-4), followed by a description of the drawings (pp. 4-5). The detailed description of the invention discusses injecting agents into the normal myocardium, which may be any vector, protein, antisense DNA, RNA, drug, cells, cells that express any therapeutic agent, bone marrow, or any other therapeutic agent capable of or useful to induce angiogenesis (pp. 5-6). Various vectors are discussed (pp. 6-7), along with braod description of promoters (p. 6) and transgenes (pp. 7-8), expression regulatory elements (p. 8), proteins (pp. 8-9), cells (p. 9), pharmaceutical compositions (p. 10-11), a listing of animals which may be treated (p. 11), amounts to administer (pp. 11-12), description of measuring cardiac function (p. 12), and methods of delivery to the myocardium (p. 12).

However, such broad description, generally in the nature of a vast list of envisioned compositions, is not enough for the Artisan to reasonably predict that the administration of cells, or cells that express angiogenic factors to the normal tissue in an ischemic heart would cause such methods as those claimed to be efficacious.

The Existence of Examples

Applicant's examples demonstrate that injection of adenoviral vectors with the VEGF165 transgene into the myocardium provide for perfusion improvements when administered to normal tissue adjacent to the ischemic tissue (EXAMPLE 1). The Examples also demonstrate that such administrations to normal tissue adjacent ischemic tissue exhibit both resting and exerted flow improvements, as well as higher capillary density (EXAMPLE 2). Applicant's EXAMPLE 2 also argues that such administration provides for better wall motion; however, the results "indicate trends toward improvement in wall motion" (p. 15, paragraph 2). How this

relates to the invention, and how these results demonstrate improved wall motion are unclear. The Examiner requests further explanation if Applicant wishes to use this information to support their claims.

However, such examples have nothing to do with the administration of cells, and the Artisan would fail to understand how such an administration would allow any cell to be administered, or whether any cell expressing an angiogenic transgene could be administered. Such is because the Artisan, as shown below, would not reasonably predict from this information that any particular cell type could engraft into the myocardium, much less express an angiogenic transgene for a long enough period of time to effect treatment, without being removed by immune responses.

The Nature of the Invention and State of the Prior Art

The invention is in the nature of somatic cell therapy and *ex vivo* gene therapy, to the myocardium of the heart.

The Art is generally not enabling of new inventions in the field of somatic cell therapy or gene therapy. Such is because, as is shown below, the specific cells used may not engraft and become part of the tissue, and the transgenic cells may not engraft in large enough amounts for a long enough period of time, while producing enough protein therefrom, to effect treatment.

The prior art demonstrates only that the only type of cell which may be injected into the myocardium and produce a therapeutic effect in ischemic heart is the mesenchymal stem cell (MSC). Such is demonstrated in U.S. Patent No. 6,387,369 to Pittenger, et al. However, Cutler, et al. (2001) Stem Cells, 19: 108-117 also makes clear in transplantations in general, that the locations in which a mesenchymal stem cell may so-engraft and effect treatment, does not equate

to the use of other stem cells, much less any cell type, due to graft-versus-host disease (e.g., CONCLUSION), and the Artisan would further conclude that such immune responses would be expected for any non-autologous therapy as it is well known in the art that allogenic and xenogenic cells also induce immune responses. The difference between Cutler and the present invention is also that of treatment of bone marrow, which is generally ablative of the immune system, and as such the instant case, the immune system remains, and therefore non-autologous therapy would be predicted to produce a graft-versus-host response, even if it is allogenic. Hence, from this, the Artisan would not reasonably predict that any cell type could be transplanted into the heart, but only autologous mesenchymal stem cells, as the cells may be rejected.

Furthermore, it is clear from Pittenger and Cutler that these stem cells are injected into the site of ischemia (Articles in general). The Artisan would recognize from this that the cells become part of the tissue into which they are injected and replace ischemic tissue. However, the Artisan would not reasonably predict that any cell, injected into another site, even adjacent could become part of and replace the ischemic tissue, as the cells are not in the ischemic tissue. Hence, the Artisan would not predict that such cells would be efficacious if not injected into the ischemic tissue.

Moreover, it is also clear in the art that engraftment is difficult and not reasonably predictable for any particular cell type. For example, even for MSCs, which have already been shown to engraft in myocardium (ABOVE), these same cells are not reasonably predicted to engraft in other tissues. To wit, Holden, et al (2002) Science, 296: 2126-29 and Orkin, et al. (2002) Nature Immunology, 3(4): 323-28, each demonstrate that engraftment is a difficult thing

to obtain, much less prove to the point of reasonable predictability (articles in their entirety). Hence, the Artisan would not reasonably predict that any particular cell type would engraft, and do so in large enough numbers to produce a therapeutic effect.

Such is further exacerbated by Applicant's claims for cells expressing an angiogenic factor. To wit, in such *ex vivo* gene therapy, targeting the tissues and doing so in large enough numbers is not reasonably predictable, as shown above, and if the angiogenic protein is not produced in large enough amounts, in the scope of the number of cells which actually target the tissue of interest, such therapy would not be efficacious.

Also, it is not reasonably predictable that delivery of any cell expressing an angiogenic factor would be efficacious if it was not delivered adjacent to the ischemic tissue and using a constitutive promoter. To wit, delivery of adenoviral vectors to the pericardium, which is not adjacent to the ischemic tissue, but still within the heart, did not demonstrate improvement in myocardial collateral perfusion models (Lazarous, et al. (1999) Cardiovasc. Res., 44: 294-302, ABSTRACT). Further, Lazarous notes, "Despite appreciable local VEGF production, however, myocardial collateral perfusion was no improved in this model" (p. 301, paragraph 3). Hence, the Artisan would not reasonably conclude that such factors would work, except when adjacent to the ischemic tissue.

Lastly, other than the use of stem cells, the Examiner fails to find any reason to expect that any other organ's cell would even produce an effect. For example, why would anyone believe that a brain cell would be efficacious in treating ischemic heart? If there is some logic to this, the Examiner requests explanation.

The Level of Predictability in the Art

Because of the art, as shown above, does not disclose enough to predict which cells could engraft into the myocardium, whether MSC implanted into normal tissue could improve ischemic myocardial tissue, whether any particular cell type would do so in high enough amounts given the particular transgene, and whether immune responses would preclude treatment, the Artisan could not predict, in the absence of proof to the contrary, that such applications would efficacious in any therapeutic treatment.

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The Amount of Experimentation Required

The Artisan, in order to determine the working embodiments, would be required, due to the factors above, to determine which types of cells could be used in such methods, due to engraftment problems, immune responses, whether MSCs implanted into normal tissue could improve ischemic tissue, whether tissues non-adjacent to the ischemic area could be treated, and

whether any beneficial effect would occur. Further experimentation would be required to determine which transgenes, expressed from which promoters, given the level of engraftment, would be efficacious in the methods.

Such experimentation is considered extensive and undue.

Conclusion

Due to the finding of undue experimentation, the claims are not enabled except for that scope provided in the initial paragraphs of this rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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